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AN INTEGRATIVE BIOMEDICAL APPROACH TO THE EVALUATION AND TREATMENT OF LUNG CANCER PATIENTS

DOCTORAL THESIS SUMMARY

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List of Published Scientific Works

1. Savencu O, Lișcu H-D, Verga N. Systems Theory in Oncology: A Narrative Review of an Integrative Framework for Understanding Cancer Complexity. Physiologia. 2025;5(4):48. doi:10.3390/physiologia5040048. https://doi.org/10.3390/physiologia5040048
2. Savencu O, Vulturar CB, Lișcu H-D, Popescu GC, Verga N. Association Between the Monocyte-to-Lymphocyte Ratio and Hemoglobin Levels in Lung Cancer Patients. In Vivo. 2026;40(4):2351–2358. doi:10.21873/invivo.70011. PMID: 42379741. https://doi.org/10.21873/invivo.70011
3. Savencu O, Lișcu H-D, Verga N. Associations Between Absolute Eosinophil and Basophil Counts and CBC-Derived Immune-Inflammatory Indices in Lung Cancer Patients: A Cross-Sectional Observational Study. Cureus – pending publication

Introduction

According to GLOBOCAN 2022 data, lung cancer represents the most frequently diagnosed cancer and the leading cause of cancer death worldwide, with approximately 2.5 million new cases and 1.8 million deaths recorded annually [1]. Despite the progress achieved in recent decades in molecular diagnostics, immunotherapy, and targeted treatments, the prognosis remains poor in advanced stages, and the clinical and biological variability among patients constitutes a persistent challenge for oncology practice.

The modern understanding of cancer recognizes it as a systemic disease, in which the dynamic interactions between the tumor and the host organism extend beyond the boundaries of the tumor microenvironment and generate biological changes detectable at the peripheral level [2]. Chronic systemic inflammation, disturbances of iron metabolism, and electrolyte imbalances are frequent phenomena in lung cancer patients, with implications for functional status, treatment tolerance, response to immunotherapy, and clinical course [2–4].

The fundamental problem addressed in this thesis derives from current oncology practice, where there is a substantial need for precise tools to evaluate patients and predict their course under treatment. An efficient strategy for developing such tools consists in using parameters that are already available, particularly the complete blood count, which is accessible in any clinical setting and at any stage of the disease, without additional costs. Analyzing the biological significance of CBC-derived indices and their relationships with other routine biological parameters may clarify how biological mechanisms are interconnected within the tumor–host relationship and may support the development of more comprehensive evaluation tools.

Although the neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR), and the platelet-to-lymphocyte ratio (PLR) have been extensively investigated as prognostic markers in oncology, their relationships with other routine biological parameters — erythropoietic parameters, minor granulocyte subpopulations (eosinophils and basophils), and serum electrolytes — remain incompletely characterized in the context of lung cancer [5–7]. This gap is relevant to clinical practice, as a deeper understanding of these relationships may help identify biological patterns with evaluative or predictive value. The theoretical framework underlying this approach — systems theory applied to oncology

and the conceptual model of the tumor–host relationship — is detailed in Chapters 1 and 2 of this thesis, within the General Part.

The central hypothesis of the research is that the biological disturbances associated with lung cancer reflect interactions among multiple subsystems of the host organism — interactions that can be indirectly detected by analyzing the relationships between peripheral biomarkers of the immune-inflammatory subsystem and biomarkers belonging to other biological subsystems, such as the erythrocyte compartment, the minor granulocyte compartment, and electrolyte homeostasis. The general objective was to investigate these relationships through three observational, retrospective, cross-sectional studies.

The statistical methodology included Spearman correlations, FDR correction (Benjamini–Hochberg procedure), multivariable regression with HC3 robust standard errors, and partial correlation analyses to evaluate the mediating role of the lymphocyte compartment. The ethical aspects of the research were conducted in accordance with the principles of the Declaration of Helsinki, and the research protocol was approved by the institutional ethics committee.

The first study demonstrated that MLR shows significant inverse associations with erythropoietic parameters, stronger than those of NLR and PLR, suggesting the involvement of the monocyte–macrophage axis in mechanisms related to erythropoiesis [8]. The second study showed that the absolute counts of eosinophils and basophils are significantly associated with immune-inflammatory indices, associations substantially mediated by the lymphocyte compartment. The third study delineated the limits of routine peripheral biomarkers in capturing the interactions between electrolyte homeostasis and the immune-inflammatory response, with the absence of robust associations representing a contribution to the understanding of tightly regulated homeostatic systems [9].

The main advantages of the research lie in the exclusive use of routine analyses, without additional costs or investigations, and in the comparative nature of the approach, which allowed the simultaneous evaluation of several inflammatory indices in relation to the same biological compartment. The main limitations derive from the retrospective, cross-sectional design, the relatively small size of the cohorts, the single-center nature of the data, and the absence of additional molecular biomarkers (hepcidin, ferritin, cytokines). Furthermore, the influence of several clinical factors with incomplete documentation —

systemic corticosteroid therapy, inflammatory comorbidities, smoking history, and ECOG performance status — could not be systematically documented in any of the three studies.

Future studies should adopt a prospective, multicenter design, incorporate additional molecular biomarkers, and investigate the predictive value of the identified associations with respect to treatment response and survival. In addition, integrating the systemic perspective into computational models of the tumor–host relationship constitutes a research direction with significant potential for advancing the understanding of lung cancer biology.

General Part of the Thesis

1. Theoretical Foundations of Systems Theory Applied to Oncology

General systems theory, initially formulated by Ludwig von Bertalanffy in the second half of the twentieth century, proposes the study of the relationships among components, of organization, and of the collective behavior of the biological whole, going beyond the limits of reductionist approaches centered on the isolated analysis of individual components [10].

Chapter 1 of the thesis synthesizes the fundamental properties of complex biological systems and their relevance to understanding oncological phenomena. Nonlinearity describes apparently disproportionate responses to biological stimuli, explaining, for example, why a point mutation in a key gene can trigger extensive oncogenic processes. Structural and functional interdependence highlights that the biological function of a component depends on the context of the network — illustrated, for instance, by the behavior of macrophages, which may exert antitumor or protumor effects depending on signals from the microenvironment. Feedback and regulatory mechanisms complete the picture, showing that tumor aggressiveness cannot be explained solely by the sum of individual genetic alterations, but rather results from the interactions among multiple biological components, such as the genome, cell signaling pathways, the microenvironment, and the immune system [9].

From the systemic perspective of the thesis, cancer can be interpreted as a complex adaptive system, and the tumor cell as a biological subsystem capable of reorganizing its internal functions in response to microenvironmental and therapeutic stimuli. From this perspective, the different intracellular compartments — the nucleus, mitochondria, cell membrane, endoplasmic reticulum, exosomes — are analyzed as interdependent biological subsystems, and properties such as metabolic reprogramming, intratumoral heterogeneity, and therapeutic resistance, as documented in the literature, are treated as emergent properties of the tumor system rather than as effects of individual molecular mechanisms [11].

The concepts of network medicine and biological modules are presented as practical extensions of the systemic perspective, with direct relevance to the interpretation of peripheral biomarkers [12]. Inflammation, metabolism, hematopoiesis, and electrolyte homeostasis are thus interpreted as distinct yet functionally integrated biological modules, whose interactions are mediated by feedback and reciprocal regulatory mechanisms.

Peripheral biomarkers are not regarded as isolated indicators, but as expressions of disturbances within interconnected biological networks — a perspective that underlies the entire research approach of this thesis.

2. The Tumor–Host Relationship and Systemic Biomarkers in Lung Cancer

Chapter 2 builds the specific conceptual framework of the thesis, integrating literature data on the components of the tumor–host relationship relevant to the three original studies. Lung cancer is characterized by a sustained systemic inflammatory response, generated by the continuous interactions among tumor cells, the associated stroma, and the host immune system. Proinflammatory cytokines — particularly IL-6, TNF-α, and IL-1β — produce systemic effects that extend beyond the local microenvironment, simultaneously influencing hematopoiesis, iron metabolism, adaptive immune function, and the homeostasis of the internal environment [2].

The lymphocyte compartment occupies a central position both clinically and methodologically. Lymphopenia is frequently observed in advanced lung cancer and reflects a systemic dysfunction of the adaptive immune response, mediated by the immunosuppressive effects of tumor-derived cytokines, the expansion of regulatory cell populations, and the cytotoxic effects of treatment. From a methodological standpoint, the lymphocyte compartment holds particular significance for CBC-derived biomarkers, since NLR, MLR, and PLR share the same denominator — lymphocytes. Any phenomenon that influences lymphocytes will simultaneously influence all three indices, regardless of variation in the myeloid or platelet components. This observation has direct implications for the interpretation of associations between other leukocyte subpopulations and inflammatory indices.

Eosinophils and basophils are presented as minor granulocyte subpopulations, with distinct immunological functions and their own dynamics in the context of tumor inflammation. Eosinophils possess direct cytotoxic mechanisms against neoplastic cells, and pretreatment peripheral eosinophilia has been associated with better responses to checkpoint inhibitor immunotherapy in NSCLC [13]. Eosinopenia, by contrast, may represent the expression of a severe systemic stress response, mediated by cortisol and proinflammatory cytokines. Basophils, although the rarest circulating leukocyte population, are capable of secreting IL-4, IL-13, and histamine, and have been identified within the microenvironment of several solid tumors, including lung adenocarcinoma [14].

The relationship between inflammation, metabolism, and erythropoiesis is analyzed through the lens of the IL-6–hepcidin–ferroportin axis [15, 16]. Stimulation of hepatic hepcidin synthesis by IL-6 leads to inhibition of ferroportin and retention of iron within the reticuloendothelial system, reducing its availability for erythropoiesis and contributing to anemia of chronic disease. The monocyte–macrophage system plays a central role in these processes, through its function in recycling iron from senescent erythrocytes and its sensitivity to inflammatory signals that alter iron distribution [17]. Electrolyte homeostasis, finally, is presented as a tightly regulated subsystem, in which the interactions with the immune system — documented predominantly at the experimental level (the role of Ca^{2+} in T-lymphocyte activation [18], of K^{+} in the functioning of immune cell ion channels [19], and of Na^{+} in modulating Th17 differentiation [20]) — may not be adequately reflected by serum electrolyte variations.

Personal Contributions

3. Working Hypotheses and General Objectives

Working Hypotheses

The general hypothesis of the thesis is that the disturbances associated with lung cancer involve interactions among multiple biological subsystems of the host organism — interactions that can be indirectly detected by analyzing the relationships between peripheral biomarkers of the immune-inflammatory subsystem and biomarkers belonging to other subsystems: the erythrocyte compartment, the minor granulocyte compartment, and electrolyte homeostasis. Three working hypotheses derive from this:

(1) MLR shows a stronger inverse association with hemoglobin and hematocrit compared to NLR and PLR, owing to the particular role of the monocyte–macrophage axis in regulating iron metabolism;

(2) The absolute counts of eosinophils and basophils show inverse associations with immune-inflammatory indices, a phenomenon predominantly mediated by covariation with the lymphocyte compartment;

(3) Serum electrolyte concentrations are associated with changes in the peripheral immune-inflammatory compartment, reflecting the interactions between electrolyte homeostasis and the systemic immune response in the context of lung cancer.

Objectives

(1) Evaluating the relationship between CBC-derived immune-inflammatory indices and erythropoietic parameters.

Purpose: To determine the extent to which MLR is associated with erythropoietic parameters, compared with NLR and PLR, as a possible indirect indicator of the involvement of monocyte/macrophage-mediated mechanisms in the anemia associated with chronic inflammation in lung cancer patients.

Method used: retrospective observational study (Study I, Chapter 4 of the summary), with Spearman correlations between inflammatory indices and erythropoietic parameters, as well as sensitivity analyses in relevant clinical subgroups.

(2) Investigating the associations between minor granulocyte subpopulations (eosinophils, basophils) and immune-inflammatory indices.

Purpose: To evaluate the association between the absolute counts of eosinophils and basophils and immune-inflammatory indices (NLR, MLR, PLR) in lung cancer patients.

Method used: retrospective observational study (Study II, Chapter 5 of the summary), with Spearman correlations, partial correlations controlled for lymphocytes, FDR correction, and multivariable regression.

(3) Evaluating the relationship between serum electrolyte concentrations and peripheral immune-inflammatory markers.

Purpose: To determine the extent to which routine serum electrolyte variations reflect the experimentally documented interactions between ionic homeostasis and immune function.

Method used: retrospective observational study (Study III, Chapter 6 of the summary), with Spearman correlations, multivariable regression, and sensitivity analysis in the subgroup without active chemotherapy.

4. General Research Methodology

All three studies share an observational, retrospective, cross-sectional design, using clinical and biological data collected in the routine practice of the MedEuropa Oradea oncology center, over the period January 2016 to December 2025. The primary data source was the complete blood count with differential (including the erythropoietic parameters — hemoglobin and hematocrit), supplemented, where applicable, with the serum electrolyte panel. Inclusion and exclusion criteria were defined separately for each study to ensure the homogeneity of the study populations and the biological relevance of the measurements used. Only adult patients (≥18 years) with a confirmed diagnosis of lung cancer and complete sets of biological measurements available for the variables of interest were included. Patients with incomplete data, duplicate records, or temporal inconsistencies between measurements were excluded. A complete-case approach was used in all studies.

The biological variables investigated can be classified by subsystem: the immune-inflammatory subsystem — total leukocytes, neutrophils, lymphocytes, monocytes, platelets, NLR, MLR, PLR; the erythrocyte compartment — hemoglobin (g/dL), hematocrit

(%); the minor granulocyte compartment — absolute eosinophils, absolute basophils, ELR (eosinophil-to-lymphocyte ratio), BLR (basophil-to-lymphocyte ratio); electrolyte homeostasis — serum sodium, potassium, calcium, magnesium, chloride; adjustment variables — age, sex, serum creatinine, active chemotherapy status at the time of sampling.

The general statistical strategy included: descriptive analysis with assessment of distribution using the Shapiro–Wilk test and graphical inspection of histograms; Spearman correlations to evaluate bivariate associations, appropriate for the non-normal distributions systematically identified across all studies; FDR correction using the Benjamini–Hochberg procedure for multiple testing, applied simultaneously to the complete set of primary tests in each study; multivariable linear regression models with logarithmic transformation of the dependent variables and HC3 robust standard errors, adjusted for age, sex, serum creatinine, and chemotherapy status; partial correlation analyses via residual regression to evaluate the mediating role of the lymphocyte compartment; sensitivity analyses in relevant clinical subgroups (without chemotherapy, NSCLC subgroup, without pulmonary metastases). All analyses were performed in Python version 3.11.

The ethical aspects of the research were conducted in accordance with the principles of the Declaration of Helsinki. Data were collected retrospectively from electronic medical records, anonymized prior to analysis, and used exclusively for scientific purposes, and the research protocol was approved by the institutional ethics committee. The retrospective nature of the study and the exclusive use of routine data did not involve additional risks for patients and did not require individual informed consent.

5. Association Between the Monocyte-to-Lymphocyte Ratio and Erythropoietic Parameters in Lung Cancer Patients

Anemia represents one of the most common hematological complications of lung cancer, with a prevalence that increases as the disease progresses. Its pathophysiology is multifactorial, including direct effects of oncological treatments, bone marrow infiltration, blood loss, and anemia of chronic disease secondary to systemic inflammation [3]. The inflammatory mechanisms contributing to anemia of chronic disease particularly involve the monocyte–macrophage system, through its role in iron recycling and its sensitivity to

inflammatory signals that alter the IL-6–hepcidin–ferroportin axis [15–17]. Although the relationship between inflammation and anemia is well documented at the mechanistic level, relatively few studies have directly investigated the relationship between CBC-derived indices and erythropoietic parameters, particularly for MLR, which has been less studied than NLR and PLR.

The study included 90 adult patients with a confirmed diagnosis of lung cancer (74 NSCLC, 12 SCLC, 4 pulmonary metastases), evaluated on an outpatient basis at the MedEuropa Oradea oncology center, with complete blood count and hemoglobin and hematocrit values determined before the initiation of radiotherapy and in the absence of active chemotherapy or immunotherapy. The mean age was 64.4 ± 7.1 years, with a male predominance (77.8%). The distribution of tumor stages was predominantly advanced (stages III–IV in 76.7% of patients). NLR, MLR, and PLR were calculated, and their associations with hemoglobin and hematocrit were evaluated using Spearman correlations.

The analysis revealed selective associations between the inflammatory indices and the erythropoietic parameters. MLR showed moderate, significant inverse correlations with hemoglobin ($\rho = -0.34$; $p = 0.001$) and hematocrit ($\rho = -0.31$; $p = 0.003$). PLR showed inverse associations of smaller magnitude (hemoglobin: $\rho = -0.24$; $p = 0.026$; hematocrit: $\rho = -0.25$; $p = 0.019$). NLR showed no significant associations with the erythropoietic parameters (hemoglobin: $\rho = -0.12$; $p = 0.251$; hematocrit: $\rho = -0.12$; $p = 0.248$). Hemoglobin and hematocrit showed a very strong positive correlation ($\rho = 0.97$; $p < 0.001$), reflecting the close physiological relationship between the two parameters. The MLR–Hb and MLR–Ht associations were robust in sensitivity analyses performed after excluding pulmonary metastases and within the NSCLC subgroup. Study I confirmed the working hypothesis.

The superiority of MLR over NLR derives from the absence of any significant association for NLR, rather than from a difference in magnitude between two significant correlations. The results are consistent with the particular involvement of the monocyte–macrophage component in the inflammatory mechanisms related to erythropoiesis: monocytes participate in recycling iron from senescent erythrocytes, and under inflammatory conditions their persistent activation favors iron retention within the reticuloendothelial compartment. Thus, MLR captures a biological dimension distinct from NLR and PLR, reflecting the involvement of the monocyte component in the disturbance of

iron metabolism and erythropoiesis in lung cancer. From a systemic perspective, the anemia observed cannot be interpreted solely as an isolated consequence of the neoplastic disease, but rather as the expression of a simultaneous disturbance across multiple interconnected biological subsystems.

6. Association Between Absolute Eosinophil and Basophil Counts and Systemic Immune-Inflammatory Indices in Lung Cancer Patients

The complete blood count includes, in addition to the major cell populations, two minor granulocyte subpopulations — eosinophils and basophils — sometimes omitted from routine clinical interpretation. Nevertheless, these cells possess distinct immunological functions with oncological relevance [21]. Eosinophils exert direct cytotoxic effects on neoplastic cells through the release of granular content and participate in the recruitment of CD8+ T lymphocytes via chemokine secretion [21]. Pretreatment peripheral eosinophilia has been associated with better responses to immune checkpoint inhibitors in NSCLC [13, 22, 23]. Basophils have been documented in association with lung cancer [14], and through the secretion of IL-4 and IL-13 they may polarize tumor-associated macrophages toward a protumor M2 phenotype [24]. However, the relationship between these subpopulations and classical immune-inflammatory indices remained uncharacterized, particularly regarding the mediating role of the lymphocyte compartment.

The study included 72 patients with primary lung cancer (squamous cell carcinoma 40.3%, adenocarcinoma 27.8%, neuroendocrine tumors 26.4%, NSCLC NOS 5.6%), evaluated pretreatment. NLR, MLR, PLR, ELR (eosinophil-to-lymphocyte ratio), and BLR (basophil-to-lymphocyte ratio) were calculated. Bivariate associations were evaluated using Spearman correlations with FDR correction (Benjamini–Hochberg procedure). To characterize the mediating role of the lymphocyte compartment, partial correlations controlled for lymphocyte count were calculated. A multivariable regression model was built for log(MLR), adjusted for active chemotherapy, age, and sex, with HC3 robust standard errors. A sensitivity analysis was performed in the subgroup of patients without active chemotherapy (n = 38).

Eosinophils showed significant inverse correlations with NLR (ρ = −0.295; p FDR = 0.024) and MLR (ρ = −0.346; p FDR = 0.012), with no significant association with PLR after FDR correction. Basophils showed a significant inverse association with NLR (ρ = −0.336; p FDR = 0.012), with no significant associations with MLR or PLR after FDR correction. Tertile analysis of basophils revealed a significant gradient for NLR (Kruskal–Wallis p = 0.014), with the lowest tertile showing significantly higher NLR values than tertiles T2 and T3. The normalized ratios ELR and BLR showed no significant associations with any immune-inflammatory index after FDR correction (all p FDR > 0.14). Both eosinophils (ρ = +0.305; p = 0.009) and basophils (ρ = +0.264; p = 0.025) covaried positively with lymphocytes. Partial correlations controlled for lymphocytes showed substantial attenuation of the eosinophil → MLR association (partial ρ = −0.143; p = 0.231; 59% attenuation) and partial attenuation of the basophil → NLR association (partial ρ = −0.233; p = 0.047; 31% attenuation). The eosinophil → MLR association withstood multivariable adjustment (β = −0.152; 95% CI: −0.250 to −0.053; p = 0.004), and active chemotherapy contributed significantly to MLR variability (β = +0.553; p = 0.002). Thus, Study II partially confirmed the working hypothesis.

These results support the hypothesis that the observed associations are predominantly mediated through the lymphocyte compartment: a tumor-related inflammatory environment that produces lymphopenia tends to be simultaneously associated with lower eosinophil/basophil counts and higher NLR/MLR values, rather than through a direct relationship between the minor granulocyte subpopulations and the myeloid components. The disappearance of the signal for ELR and BLR upon normalization for lymphocytes is consistent with this hypothesis. Lymphopenia may represent the central node of peripheral leukocyte system reorganization in lung cancer, simultaneously influencing multiple compartments of innate and adaptive immunity.

7. Relationship Between Serum Electrolyte Concentrations and Immune-Inflammatory Markers in Lung Cancer Patients

Electrolytes participate in essential biological processes with immunological relevance: calcium mediates T-lymphocyte activation through intracellular fluxes and

activation of the calcineurin–NFAT pathway [18]; potassium influences the functioning of immune cell ion channels and, at elevated extracellular concentrations (characteristic of the tumor microenvironment), may inhibit T-lymphocyte effector function [18, 19]; sodium may modulate Th17 lymphocyte differentiation [20]; magnesium contributes to lymphocyte proliferation and activation; neutrophils use chloride ions in generating hypochlorous acid via myeloperoxidase. Electrolyte disturbances — hyponatremia (common in SCLC due to SIADH), hypercalcemia, and potassium dysregulation — are frequent complications in lung cancer [4]. Nevertheless, the relationships between serum electrolytes and peripheral immune-inflammatory markers remain insufficiently investigated in lung cancer.

The study included 59 patients with lung cancer (NSCLC 71.2%, SCLC 23.7%), evaluated prior to the initiation of radiotherapy, with complete blood count and simultaneous serum determinations of sodium, potassium, calcium, magnesium, and chloride. Spearman correlations were evaluated between electrolytes and leukocyte populations (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and separately, immune-inflammatory markers (NLR, MLR, PLR). Multivariable regression models for log(NLR), log(MLR), and log(PLR) included standardized sodium and potassium, with adjustment for age, sex, serum creatinine, and active chemotherapy. FDR correction was applied to all secondary multiple analyses. A sensitivity analysis was performed after excluding patients undergoing active chemotherapy (n = 31).

Correlation analyses revealed no significant associations between any of the electrolytes investigated and the immune-inflammatory markers NLR, MLR, or PLR. Most Spearman coefficients had values close to zero. The only association that reached the nominal threshold of statistical significance was between serum calcium and basophil count ($\rho = -0.334$; $p = 0.046$), which did not remain significant after FDR correction. The multivariable regression models did not identify electrolytes as significant independent predictors for any immune-inflammatory index, with the exception of active chemotherapy, which remained independently associated with higher MLR values ($\beta = +0.534$; $p = 0.006$). The sensitivity analysis in the subgroup without active chemotherapy confirmed the absence of robust relationships (all correlations had $p > 0.05$). Comparison of immune-inflammatory markers according to chemotherapy status revealed significantly higher values of MLR (0.53 vs. 0.34; $p = 0.008$) and monocytes (750 vs. 600/μL; $p = 0.018$) in patients undergoing active chemotherapy. Thus, Study III did not confirm the working hypothesis.

The absence of consistent associations does not negate the existence of biological interactions between electrolyte homeostasis and the immune-inflammatory response, but rather suggests that these are not adequately reflected by the variations in serum electrolytes measured in routine clinical practice. Serum electrolyte concentrations are maintained within relatively narrow limits by complex homeostatic mechanisms — renal regulation, endocrine axes, active membrane transport — which help limit extracellular variation even in the presence of pathological disturbances. The values measured in peripheral blood therefore reflect both the influence of pathological processes and the efficiency of compensatory regulatory systems. Peripheral immune-inflammatory biomarkers and serum electrolytes appear to be expressions of distinct biological processes, insufficiently coupled at the level of accessible routine parameters. The experimentally documented interactions between electrolytes and immune function occur predominantly at the level of intracellular ionic distribution and transmembrane fluxes, which are inaccessible through conventional serum measurements.

Conclusions and Personal Contributions

Conclusions

The research achieved its proposed objectives: for each of the three biological subsystems investigated, the relationships with peripheral immune-inflammatory markers were characterized, identifying both significant associations — in the case of the erythrocyte compartment and the minor granulocyte compartment — and the absence of robust relationships, in the case of electrolyte homeostasis.

By integrating the results of the three studies, the thesis proposes a systemic perspective on the tumor–host relationship in lung cancer, in which CBC-derived biomarkers are used as indirect indicators of the interactions between distinct biological subsystems of the organism. This perspective, grounded in the systems theory presented in Chapter 1, may serve as a starting point for future studies with a prospective design, larger cohorts, and additional molecular biomarkers (hepcidin, ferritin, IL-6, cytokine profiling, detailed immunological phenotyping).

The main advantages of the research lie in the exclusive use of parameters already available, without additional costs or investigations relative to routine oncology practice, and in the comparative nature of the approach — simultaneously evaluating several inflammatory indices in relation to the same biological compartment. The main limitations derive from the retrospective, cross-sectional design, which does not allow the establishment of causality or the direction of temporal relationships, from the relatively small size of the cohorts, and from the single-center nature of the data, which may limit the generalizability of the conclusions. The lack of additional molecular biomarkers (hepcidin, ferritin, erythropoietin, cytokines, intracellular ionic distribution) limits the ability to mechanistically characterize the identified relationships. Furthermore, the influence of several clinical factors with incomplete documentation — systemic corticosteroid therapy, inflammatory comorbidities, smoking history, and ECOG performance status — could not be systematically documented in any of the three studies.

Future studies should adopt a prospective, multicenter design, incorporate additional molecular biomarkers, and include longitudinal evaluations. Future directions also include the prospective validation of the identified associations and the exploration of their predictive value for treatment response. For electrolyte homeostasis, evaluations of

intracellular ionic distribution and measurements of transmembrane ionic fluxes are needed, going beyond the limits imposed by the strong homeostatic regulation of serum electrolytes. Integrating the systemic perspective into computational and mathematical models of the tumor–host relationship represents a direction with significant potential for understanding lung cancer biology.

Personal Contributions

The personal contributions of this thesis derive from the systematic investigation of the tumor–host relationship in lung cancer through the analysis of the associations between the immune-inflammatory subsystem — characterized by CBC-derived markers (NLR, MLR, PLR) — and three distinct biological subsystems of the host organism: the erythrocyte compartment (hemoglobin and hematocrit), the minor granulocyte compartment (absolute eosinophils and basophils, ELR, BLR), and electrolyte homeostasis (sodium, potassium, calcium, magnesium, chloride).

The first study demonstrated that MLR shows significant inverse associations with erythropoietic parameters (Hb: $\rho = -0.34$; Ht: $\rho = -0.31$), stronger than those of NLR (not significant) and PLR, contributing to the characterization of the differential involvement of the monocyte–macrophage axis in mechanisms related to erythropoiesis. The associations were robust in sensitivity analyses within the NSCLC subgroup and after excluding pulmonary metastases.

The second study yielded two complementary contributions: (a) demonstrating that the absolute counts of eosinophils and basophils show significant inverse associations with immune-inflammatory indices (eosinophils → NLR: $\rho = -0.295$; eosinophils → MLR: $\rho = -0.346$, withstanding multivariable adjustment; basophils → NLR: $\rho = -0.336$), and (b) showing that the relevant information resides in the absolute values rather than in the ratios normalized to lymphocytes (ELR, BLR — not significant after FDR), with the associations being substantially mediated through the lymphocyte compartment (attenuation: eosinophils → MLR, 59%; basophils → NLR, 31%), suggesting that lymphopenia represents the central node of peripheral leukocyte system reorganization in lung cancer.

The third study delineated the limits of routine peripheral biomarkers in capturing the interactions between electrolyte homeostasis and the immune-inflammatory response in lung

cancer; the absence of robust associations after FDR correction represents, in itself, a contribution to the understanding of tightly regulated homeostatic systems.

The results of the three studies were integrated into a unified systemic perspective on the tumor–host relationship in lung cancer, proposing CBC-derived biomarkers as indirect indicators of the interactions between distinct biological subsystems of the organism.

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